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Dissipation, terminal residues and risk assessment of fluopicolide and its metabolite in cucumber under field conditions

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Abstract In this study, the dissipation, terminal residue levels, and risk assessment of fluopicolide and its metabolite (2,6-dichlorobenzamide) in cucumber and soil under field conditions were investigated. An analytical method for the simultaneous quantification of fluopicolide and its metabolite in cucumber and soil using gas chromatography coupled with electron capture detection (GC-ECD) was developed. Recoveries were between 78 and 111 %, with relative standard deviations (RSDs) from 1.6 to 10.2 % at different spiked levels (0.01, 0.025, 0.5, and 2 mg kg^{-1}). The limit of quantification (LOQ) was 0.01 mg kg^{-1}. Fluopicolide exhibited half-lives ranging from 2.0 to 3.3 days and 35 to 63 days, in cucumber and soil under field ecosystem, respectively. The results suggested that the degradation of fluopicolide to 2,6-dichlorobenzamide was quite limited. During harvest, the terminal residues of fluopicolide and its metabolite were both below 0.13 mg kg^{-1}, which were lower than the established temporary maximum residue limits (MRLs), 0.5 mg kg^{-1}. The risk quotients (RQs) ranged from 0.0033 to 0.0078, which showed low risk for different groups of people in China. The present study may provide guidance on reasonable use of this pesticide and serve as a reference for establishment official MRLs in China.

Highlights 1. Dissipation of fluopicolide and its metabolite in cucumber were firstly investigated.
2. Terminal residue levels were obtained with recommended dose and PHI.
3. Risk assessment for different groups of people in China was done.

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Introduction

Fluopicolide (2,6-dichloro-*N*-[[3-chloro-5-(trifluoromethyl)-2-pyridinyl]methyl] benzamide), developed by Bayer CropScience (Latorse et al. 2006), is a novel fungicide of the new chemical class, acyl picolide. It exhibits a high level of controlling activity against oomycete organisms, which cause a number of economically important diseases in a variety of crops (Jackson et al. 2010; Shin et al. 2010; Wang et al. 2014a; b; Kousik et al. 2011). In addition, fluopicolide shows no cross-resistance with other fungicide groups (Latorse et al. 2006; Toquin et al. 2006). Fluopicolide and its metabolite, 2,6-dichlorobenzamide, are included in the definition of residues for the estimation of the dietary intake by the Joint Meeting on Pesticide Residues (JMPR). Furthermore, 2,6-dichlorobenzamide is more toxic than its parent compound. The acceptable daily intake (ADI) of 2,6-dichlorobenzamide is 0.02 mg kg^{-1}, while the ADI of fluopicolide is 0.08 mg kg^{-1} (http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Report09/Fluopicolide.pdf). As a consequence, the monitoring of the metabolite is of equally great significance with its parent.

The MRLs are set by international organizations and governments to protect the public health safety from the harmful effects of pesticide. FAO, European Union, USA, and Canada have established MRLs for fluopicolide in cucumber which was 0.5 mg kg^{-1} (www.globalmrl.com). However, until now, there have been scarce validated data to support MRL of fluopicolide in cucumber in China. Human exposure to pesticides through food consumption can be estimated using quantitative exposure assessments (Tsakiris et al. 2015). The outputs of risk assessment are the scientific basis for risk management decisions and option analysis (FAO/WHO, Food Standards Programme, Codex Alimentarius Commission 2008). In general, food consumption is not the same across cultures due to various dietary structures in different countries. Therefore, the risk assessment of fluopicolide and its metabolite exposure in Chinese consumers is in urgent need.

To the best of our knowledge, there are few studies regarding methods for analyzing fluopicolide and its metabolite simultaneously in cucumber and soil. No published studies are available concerning the residues of fluopicolide and its metabolite in cucumber and the potential dietary risks to date. Previous studies put focus on the fungicidal activity of fluopicolide on different crops such as squash (Jackson et al. 2010), pepper (Shin et al. 2010; Chen and Wang 2009), potato, tomato (Wang et al. 2014a; b), watermelon (Kousik et al. 2011), and cucumber (Wang et al. 2014a; b; Lu et al. 2011; Zhu et al. 2012; Yan et al. 2013), and a few studies reported the presence of parent residues in tomato (Sahoo et al. 2014) and grape (Mohapatra et al. 2011; Paramasivam and Chandrasekaran 2013).

This study aims (1) to develop an efficient analytical method to simultaneously determine the fluopicolide and its metabolite in cucumber and soil, (2) to evaluate the dissipation rate and residue level of fluopicolide and its metabolite in cucumber and soil under field condition, and (3) to investigate the potential dietary risk assessment of fluopicolide for different groups of people in China based on the residual levels. The results provide guidance on the proper and safe use of fluopicolide and serve as a reference for establishing associated MRLs in China.

Materials and methods

Chemicals

Reference standards of fluopicolide and 2,6-dichlorobenzamide (both of the purities were 98.5 %) were obtained from Dr. Ehrenstorfer Gmbh. A mixed formulation of a suspension concentrate (SC) containing 5 % fluopicolide and 40 % chlorothalonil was purchased from Ruidefeng Pesticides (Guangdong, China). Analytical grade of acetonitrile, acetone, sodium chloride, and petroleum ether was purchased from Beijing Chemical Reagent Co., Ltd. (Beijing, China). Petroleum ether was distilled before use and fractioned at 60–70 °C. The Florisil solid-phase extraction (SPE) column (1 g/6 mL) was purchased from ANPEL Laboratory Technologies, Inc. (Shanghai, China).

Field trials study

The field trials were designed according to the "Guideline on Pesticide residue Trials" and "Standard Operation Procedures on Pesticide Registration Residue Field Trials" in 2004 and 2007, respectively (NY/T 788-2004, P. R. China; ICAMA, Institute for the Control of Agrochemicals, Ministry of Agriculture 2007). The supervised field trials were performed in Beijing (116.1′ E, 40.0′ N), Henan (113.6′ E, 34.7′ N) and Anhui (117.0′ E, 33.6′ N) in 2014. Each field trial consisted of three replicate test plots and a control plot (15 m^2 for each plot), and each plot was separated by a buffer area. None of the plots had been treated with fluopicolide and chlorothalonil in the past.

To investigate the dissipation of fluopicolide in cucumber and soil, the 45 % fluopicolide chlorothalonil SC was applied with dosages of fluopicolide 1215 and 9004.5 g a. i. ha^{-1} (gram of active gradient per hectare), respectively. Pesticide applications were started when the cucumber was halfway to ripeness. Representative cucumber samples were collected from each plot after spraying on days 0 (2 h), 1, 3, 5, 7, 10, and 14, while soil samples were collected on days 0 (2 h), 1, 3, 5, 7, 10, 14, 21, 30, 45, and 60.

For the terminal residue experiment on cucumber, the 45 % SC was applied at two dosage levels of 607.5 g a. i. ha^{-1} (recommended dosage) and 911.25 g a. i. ha^{-1} (1.5 times the recommended dosage). Each dosage level was sprayed two and three times with interval of 7 days between each application. Representative cucumber samples were collected at intervals of 1, 2, 3, and 5 days after the last spraying.

All the samples were transported into labeled polyethylene bags and stored at −20 °C for further analysis.

Pretreatment method

The cucumber samples were crushed thoroughly in a blender. The soil samples were crushed with a hammer and passed through a 40-mesh screen. Briefly, homogenized sample (10.00 ± 0.01 g) was transferred into a 50-mL centrifuge tube (5 mL of distilled water was added to soil sample) and extracted with 20 mL of acetonitrile by ultrasonic for 15 min. Afterwards, 6 g of sodium chloride was added and the tube was shaken vigorously for 1 min and centrifuged at 3000 rpm for 5 min. A portion (10 mL) of supernatant was evaporated to near dryness using a vacuum rotary evaporator at 35 °C.

For the cleanup, the SPE cartridge was previously conditioned with 5 mL of petroleum ether. The concentrated extracts were fifth washed with 5 mL of petroleum ether/acetone (8:2, *v*/*v*) and transferred to the cartridge. The eluent was collected and concentrated to dryness on a vacuum rotary evaporator at 35 °C and dissolved in 2.5 mL of petroleum ether/acetone (8:2, *v*/*v*) for GC-ECD analysis.

GC-ECD analysis

Fluopicolide was determined using an Agilent 7890A gas chromatography equipped with an electron capture detection. Separation was carried out on a DB-35MS (30 m × 0.32 mm × 0.25 μm) capillary column. The injector was operated at 260 °C with an injection volume of 1 μL. The oven temperature was programmed to ramp from 100 °C, was raised to 260 °C at 10 °C min^{-1} for 4 min, and then raised to 280 °C at 20 °C min^{-1} for 6 min. Nitrogen was used as the carrier gas at a flow rate of 1 mL min^{-1}. The detector was maintained at 300 °C. The approximate retention time of fluopicolide and 2,6-dichlorobenzamide was 17.8 and 11.1 min, respectively.

Dissipation kinetics

The dissipation dynamics and half-lives of fluopicolide and its metabolite in cucumber and soil were determined using the first-order kinetics equations:

$$C = C_0 e^{-kt}$$
$$t_{1/2} = \frac{\ln 2}{k}$$

where C (mg kg^{-1}) is the concentration at time t (days) after treatment, C_0 (mg kg^{-1}) is the initial concentration, and k is the first-order rate constant (day^{-1}) (Li et al. 2008).

Exposure assessment

The dietary exposure and risk assessment were calculated as follows:

$$\mathrm{EDI} = \frac{F_i \times \mathrm{RL}_i}{\text{mean body weight}}$$

where EDI is the estimated daily intake (mg kg^{-1}, bw), F_i is the food consumption data (g day^{-1}), and RL_i is the residue level for the commodity (mg kg^{-1}). Results under the LOQ of the analytical methods used for intake calculations were taken as LOQ values.

$$\mathrm{RQ} = \frac{\mathrm{EDI}}{\mathrm{ADI}}$$

where RQ is the risk quotient, ADI is the acceptable daily intake (mg kg^{-1}, bw). An RQ value that is higher than RQ = 1 indicated that the risk of pesticide for humans is unacceptable. By contrast, an RQ value that is less than RQ = 1 represents minimal risk to humans (Lozowicka et al. 2014; Institute of Quality Standards and Testing Technology for Agro-products Chinese Academy of Agricultural Science 2007; Zhang et al. 2009).

Results and discussion

Analytical method validation

Fluopicolide has been previously analyzed by GC equipped with different detectors such as mass spectrometry (MS) (Paramasivam and Chandrasekaran 2013), ECD (Mohapatra et al. 2011; Sahoo et al. 2014; Fan et al. 2014), or high-performance liquid

Table 1 Average recoveries and RSDs of fluopicolide and 2,6-dichlorobenzamide in cucumber and soil (n = 5)

Pesticide	Cucumber			Soil		
	Spiked level (mg kg^{-1})	Average recovery (%)	RSD (%)	Spiked level (mg kg^{-1})	Average recovery (%)	RSD (%)
Fluopicolide	0.01	96	10.2	0.01	105	4.7
	0.025	87	6.3	0.025	106	2.4
	0.5	103	3.8	0.5	99	2.2
	2	104	2.2	2	105	4.4
2,6-Dichlorobenzamide	0.01	108	9.5	0.01	108	4.8
	0.025	83	7.0	0.025	100	3.6
	0.5	100	5.0	0.5	94	1.6
	2	107	2.5	2	102	2.6

chromatography coupled with ultraviolet detector (HPLC-UV) (Zhang et al. 2011). However, no information on the analysis of metabolite was available. Furthermore, none of them regard methods for analyzing fluopicolide and its metabolite simultaneously in cucumber and soil. In the present study, fluopicolide and its metabolite were determined by GC-ECD, while the accuracy, precision, LOQs, and linearity of the method were evaluated. The accuracy and precision of the measurements were expressed in terms of recoveries and RSDs at different spiked levels (0.01, 0.025, 0.5, and 2 mg kg^{-1}) in cucumber and soil. The recoveries of fluopicolide and its metabolite for cucumber and soil were in the range of 78–117 % and 92–111 % respectively, with RSDs between 1.6 and 10.2 % (Table 1). The LOQs of both fluopicolide and its metabolite were estimated to be 0.01 mg kg^{-1} for cucumber and soil. Good linearity was obtained for fluopicolide and 2,6-dichlorobenzamide within 0.01–0.5 mg L^{-1} using matrix matched standards, and the coefficients of determination (R^2) were all higher than 0.99. The results confirmed that the method is sufficiently reliable for pesticide analysis in this study (OECD, Organization for Economic Co-operation and Development 2007).

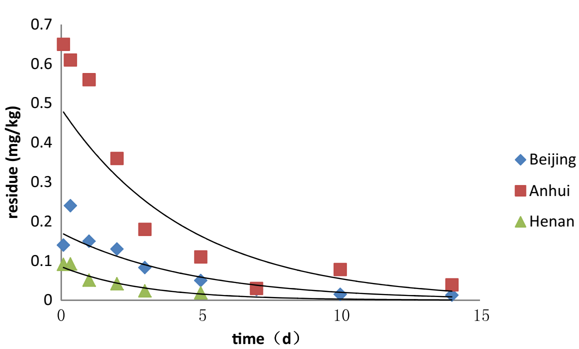

Fig. 1 Dissipation curves of fluopicolide in cucumber under field conditions

Dissipation of fluopicolide and its metabolite

Dissipation of fluopicolide and its metabolite in cucumber

The dissipation study is an important part for full evaluation and would be helpful for the proper and safe use of pesticide. The dissipation curves of fluopicolide in cucumber under field conditions are shown in Fig. 1. The initial concentrations of fluopicolide in cucumber were 0.17, 0.49, and 0.09 mg kg^{-1} with half-lives of 3.3, 3.2, and 2.0 days for Beijing, Anhui, and Henan, respectively. Sahoo et al. (2014) discovered that the half-lives of fluopicolide were 2.6 and 3.2 days in tomato. Mohapatra et al. (2011) measured fluopicolide

Table 2 Dissipation regressive equation, correlation coefficient (r) and half-lives ($t_{1/2}$) of fluopicolide in cucumber and soil

Matrix	Location	Equation	r	$t_{1/2}$ (day)
Cucumber	Beijing	$C = 0.17\ e^{-0.21T}$	−0.9638	3.3
	Anhui	$C = 0.49\ e^{-0.22T}$	−0.8788	3.2
	Henan	$C = 0.085\ e^{-0.34T}$	−0.9585	2.0
Soil	Beijing	$C = 0.034\ e^{-0.011T}$	−0.8184	63
	Anhui	$C = 0.036\ e^{-0.020T}$	−0.9262	35
	Henan	$C = 0.68\ e^{-0.016T}$	−0.9486	43

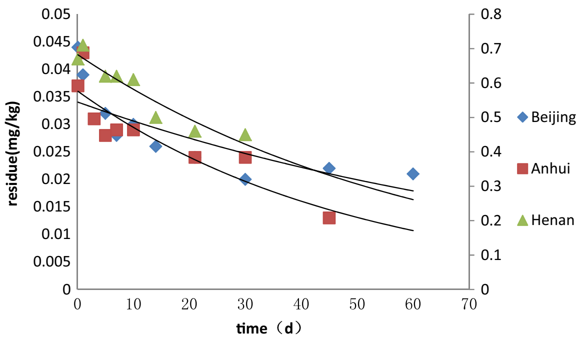

Fig. 2 Dissipation curves of fluopicolide in soil under field conditions (the *y* coordinate on the *left* is for Beijing and Anhui, the *y* coordinate on the *right* is for Henan)

half-lives of 10.2 and 12.3 days in grape berries. The difference in rate of dissipation may be caused by different growth dilution factor of crops. The residues of 2,6-dichlorobenzamide were below 0.01 mg kg^{-1}. The minor metabolite identified in this experiment indicated that fluopicolide was not metabolized to any great extent in cucumber, which agrees with previous reports (http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Report09/Fluopicolide.pdf). The dissipation regressive equations, correlation coefficient (*r*), and half-lives (*t*1/2) of fluopicolide in cucumber are shown in Table 2.

Dissipation of fluopicolide and its metabolite in soil

Residues of pesticide in soil may persist for a long time and pose a serious threat to soil ecosystem, human health, and non-target animals. Therefore, the field dissipation studies are of great meaning to ensure environmental and human health (You et al. 2014). The initial concentrations of fluopicolide in soil were 0.03, 0.04, and 0.68 mg kg^{-1} with half-lives of 63, 35, and 43 days

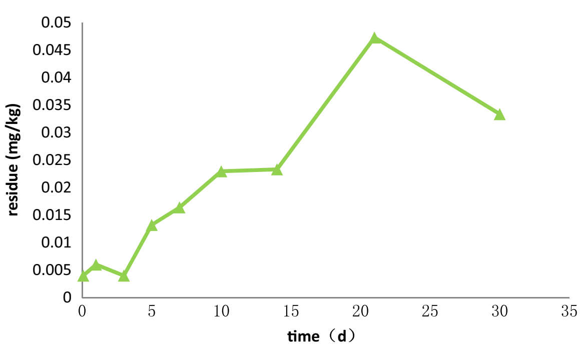

Fig. 3 Dissipation curves of metabolite in soil under field conditions in Henan

for Beijing, Anhui, and Henan, respectively (Table 2). The dissipation curves of fluopicolide in soil under field conditions are shown in Fig. 2. These results agree with previous reports that fluopicolide is considered to be persistent in soil (http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Report09/Fluopicolide.pdf). The different initial residue of fluopicolide may be a result of different ways of application. Although spraying is used in three sites, the different habits of sprayers may lead to distinct residue. In addition, the enormous difference of dissipation rate in cucumber and soil may be due to the growth dilution factor of cucumber. The different half-lives of fluopicolide between sites may be due to many factors, such as precipitation, temperature, humidity, and so on (Choi et al. 2009; Chen and Wan 1997). Moreover, the residues of 2,6-dichlorobenzamide were lower than 0.01 mg kg^{-1} in Beijing and Anhui. The data in Henan showed a tendency described as an "increase-decrease," which is shown in Fig. 3. The residue was relatively low with an initial residue of <0.01 mg kg^{-1}, while the maximum amount of metabolite was 0.05 mg kg^{-1} after 21 days of application. It could be concluded that the parent compound was the major component of the residues. The metabolization to 2,6-dichlorobenzamide is relatively unobvious, which was in agreement with the report of FAO.

Terminal residue levels

The terminal residues of fluopicolide in cucumber at harvest time are summarized in Table 3. All of the terminal residues of fluopicolide are below 0.13 mg kg^{-1}, lower than the established MRLs. The results suggest that the residue levels depend on application rates, the number of application, and pre-harvest intervals (PHI). The lower dosage, increasing PHI, and application frequencies result the residue levels to decrease (Malhat et al. 2013). On the other hand, the terminal residues of 2,6-dichlorobenzamide were below 0.01 mg kg^{-1}.

Exposure risk assessment

Risk assessment for different groups of people is investigated in this study, based on typical food (light-colored vegetables) consumption in China (Jin 2008; Liu 2014). The fluopicolide intakes were estimated using the supervised trials median residue (STMR) to evaluate

Table 3 Terminal residues of fluopicolide in cucumber

Application rate (g a. i. ha^{-1})	Number of applications	HI	Residue levels (mg kg^{-1})
607.5	2	1	0.030–0.056
		2	0.022–0.041
		3	0.015–0.035
		5	0.010–0.032
	3	1	0.037–0.084
		2	0.032–0.064
		3	0.029–0.037
		5	0.015–0.043
911.25	2	1	0.043–0.130
		2	0.039–0.084
		3	0.033–0.048
		5	0.023–0.042
	3	1	0.041–0.110
		2	0.032–0.059
		3	0.036–0.067
		5	0.021–0.061

long-term health risks to consumers based on methods recommended by the World Health Organization (WHO) (GME/Food 2012). The ADI values for fluopicolide and 2,6-dichlorobenzamide are 0.08 and 0.02 mg kg^{-1} (http://www.fao.org/fileadmin/templates/agphome/documents/Pests_Pesticides/JMPR/Report09/Fluopicolide.pdf).

The terminal residue levels in cucumber followed a trend in which shorter PHI led to more residues. Thus, the risk should be low if the risk assessment of shortest PHI (1 day) is acceptable. At PHI of 1 day, the residues of fluopicolide are as follows: 0.030, 0.032, 0.037, 0.038, 0.039, 0.041, 0.043, 0.044, 0.045, 0.047, 0.047, 0.048, 0.048, 0.050, 0.051, 0.051, 0.053, 0.056, 0.056, 0.059, 0.061, 0.063, 0.065, 0.073, 0.075, 0.079, 0.084, 0.097, 0.097, 0.100, 0.100, 0.110, 0.110, 0.110, 0.120, and 0.130 mg kg^{-1}. All the terminal residues of 2,6-dichlorobenzamide were below 0.01 mg kg^{-1}. The RL for fluopicolide and its metabolite are 0.056 and 0.01 mg kg^{-1}, respectively, according to the STMR of residues.

Table 4 Risk assessment of fluopicolide and its metabolite after 1 day application for different groups of people in China

Age	Body weight (kg)	Sex	Consumption of light-colored vegetables (g day^{-1})	EDI (mg kg^{-1}, bw)		RQ		
				Fluopicolide	Metabolite	Fluopicolide	Metabolite	Total
2–3	12.7	M	82.7	0.00036	0.00007	0.0046	0.0033	0.0078
		F	82.2	0.00036	0.00006	0.0045	0.0032	0.0078
4–6	16.5	M	105.8	0.00036	0.00006	0.0045	0.0032	0.0077
		F	101.8	0.00035	0.00006	0.0043	0.0031	0.0074
7–10	22.3	M	137.5	0.00035	0.00006	0.0043	0.0031	0.0074
		F	132.6	0.00033	0.00006	0.0042	0.0030	0.0071
11–13	34.05	M	156.6	0.00026	0.00005	0.0032	0.0023	0.0055
		F	155.3	0.00026	0.00005	0.0032	0.0023	0.0055
14–17	45.95	M	178.9	0.00022	0.00004	0.0027	0.0019	0.0047
		F	156.0	0.00019	0.00003	0.0024	0.0017	0.0041
18–29	55.25	M	202.2	0.00020	0.00004	0.0026	0.0018	0.0044
		F	186.2	0.00019	0.00003	0.0024	0.0017	0.0040
30–44	60.3	M	206.5	0.00019	0.00003	0.0024	0.0017	0.0041
		F	192.8	0.00018	0.00003	0.0022	0.0016	0.0038
45–59	60.05	M	211.4	0.00020	0.00004	0.0025	0.0018	0.0042
		F	194.9	0.00018	0.00003	0.0023	0.0016	0.0039
60–69	57.95	M	187.7	0.00018	0.00003	0.0023	0.0016	0.0039
		F	170.8	0.00017	0.00003	0.0021	0.0015	0.0035
≥70	54.75	M	187.7	0.00018	0.00003	0.0022	0.0016	0.0038
		F	170.8	0.00016	0.00003	0.0019	0.0014	0.0033

M male, *F* female

The risk assessment for different groups of people in China associated with fluopicolide and its metabolite residues in cucumber is listed in Table 4. As shown, the RQ values of fluopicolide and its metabolite in cucumber after 1 day of application were in the range of 0.0019–0.0046 and 0.0014–0.0033, respectively. The total RQ values by adding two parts together ranged from 0.0033 to 0.0078, which were significantly lower than RQ = 1. These results implied that the long-term health risks exposure to fluopicolide and its metabolite residues through cucumber at recommended dosage and PHI is relatively low.

Conclusion

An efficient analytical method to simultaneously determine the fluopicolide and its metabolite in cucumber and soil was developed. The dissipation rate under field conditions were evaluated, which indicated that fluopicolide was not metabolized to any great extent in cucumber and soil. The trial results showed that fluopicolide was susceptible to dissipate with half-lives ranged from 2.0 to 3.3 days and 35 to 63 days, in cucumber and soil under field ecosystem, respectively. The terminal residues of fluopicolide and its metabolite were both below 0.13 mg kg^{-1}. Based on the terminal residues, the risk assessment for different groups of people in China was investigated. The total RQ values were significantly lower than RQ = 1, indicating the long-term health risk is relatively low. Results of this study could provide guidance on reasonable use of this pesticide and serve as a reference for the establishment of MRL in China.

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